Epitomes

Important Advances in Clinical Medicine

Pathology

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in pathology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in pathology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pathology of the California Medical Association, and the summaries were prepared under its direction.

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Human Prion Diseases

PRIONS ARE the pathogenic agents of a group of dementing diseases associated with the production of a unique amyloid protein called prion protein (PrP). Prion diseases are novel in that they are both transmissible, or infectious, and hereditary. These diseases are known by a variety of synonyms, including human spongiform encephalopathy, "slow" (unconventional) viral infections, and transmissible dementias.

Prion diseases are linked by several elements. The disease is limited to the brain; there is a lengthy asymptomatic period lasting years or decades; they have a progressive, uniformly fatal clinical course, without remission; they are transmissible to other mammals; and no specific clinical diagnostic tests or therapy exist.

Prion diseases are characterized mostly by spongiform changes in the brain, with varying degrees of PrP amyloid deposition, gliosis, and neuronal loss; there is no notable host inflammatory response.

Prions are highly resistant to inactivation by procedures that kill viruses and bacteria by denaturing nucleic acids, but they are inactivated by procedures that denature proteins, including 1N sodium hydroxide or hypochlorite solutions and autoclaving. Prion protein is a sialoglycoprotein encoded in DNA (but devoid of any nucleic acid) that undergoes a series of posttranslational modifications to produce an abnormal isoform; this polymerizes to form PrP amyloid. Although the precursor molecule of PrP is found in most human tissues, its normal function has yet to be elucidated.

Four human prion diseases are recognized: Creutzfeldt-Jakob disease, kuru, Gerstmann-Straussler-Scheinker syndrome, and fatal familial insomnia. Whereas the clinical symptoms vary, including dementia, ataxia, myoclonus, and insomnia, they are thought to represent variations of the same disease process.

The Gerstmann-Straussler-Scheinker syndrome and fatal familial insomnia are exceedingly rare diseases found in familial clusters, being transmitted in an autosomal dominant manner. Recent evidence indicates that both diseases are caused by several different single-codon substitutions in the PrP gene. These germline mutations result in a slightly abnormal PrP molecule, the presence of which is always lethal.

Kuru is a fascinating disease localized to the Fore region in New Guinea that has been shown to be transmitted by ritualistic cannibalism. The eradication of cannibalism should result in the extermination of the disease; no new cases have developed in persons born since cannibalism ceased. Hence, kuru appears to be an orally transmitted infection.

Creutzfeldt-Jakob disease is, by far, the most common prion disease, with an incidence of about 1 case per million people per year. The most dramatic cases of Creutzfeldt-Jakob disease are those wherein the infection has been iatrogenically transmitted, such as by corneal grafts, intracranial electrodes, cadaveric dura mater grafts, and the intravenous administration of growth hormone derived from pooled cadaveric pituitary glands. Also, well-defined familial clusters of Creutzfeldt-Jakob disease exist, such as in Libyan Jews, in whom the disease is transmitted in an autosomal dominant manner like the Gerstmann-Straussler-Scheinker syndrome or fatal familial insomnia. Most cases of Creutzfeldt-Jakob disease, however, are sporadic and thought to represent random mutations of the PrP gene.

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Hepatitis C Screening and Blood Safety

BLOOD TRANSFUSION IS now safer because of routine screening for the antibody to hepatitis C virus (anti-HCV). The risk of posttransfusion non-A, non-B hepatitis has dropped from as high as 1 in 100 to less than 1 in 3,300 per unit received since May 1990 when "first-generation" enzyme immunoassay (EIA-1) screening began. Although hepatitis C virus (HCV) is not the only virus capable of causing posttransfusion non-A, non-B hepatitis, it is thought to account for at least 90% of cases. Further improvement in safety is expected with the "second-generation" methodologic enzyme immu-

noassay (EIA-2), which replaced EIA-1 in March 1992. Enzyme immunoassay 2 has improved specificity over EIA-1 with no loss of sensitivity, yielding fewer "false-positive" results, that is, reactivity without infection, based on follow-up studies of transfusion recipients and using "confirmatory" testing.

Investigational confirmatory techniques consist of an antibody detection using a modified Western blot (the recombinant immunoblot assay), a neutralization assay, and direct testing for HCV RNA by polymerase chain reaction. Blood specimens reactive by EIA-1 or EIA-2 have been shown to correlate with disease in the transfusion setting. Although the 40% to 70% falsely reactive rate with EIA-1 has been reduced significantly (to less than 30%) by the use of EIA-2, research efforts for improved "third-generation" techniques (still based on nonstructural proteins) are already under way. In addition, the control of specimen storage and handling is critical for valid testing.

More than 30 million units of donated blood have been screened with the EIA-1 anti-HCV test, resulting in the exclusion of between 120,000 and 330,000 (0.4% to 1.1%) blood donors who were unknowingly anti-HCV–reactive. Because nearly 50% of persons infected by HCV have asymptomatic but persistent liver damage, including chronic active hepatitis, cirrhosis, and even hepatocellular carcinoma, research to minimize or interrupt the natural course of this disease is indicated. Asymptomatic former blood donors provide an identified pool of potential subjects who would be directly benefited by such research efforts. Transfusion recipients of blood donated in 1992 can expect more than a 20-fold reduction in the risk of posttransfusion hepatitis because blood is screened for anti-HCV.

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Acquired Immunodeficiency Syndrome Vaccines

THE DEVELOPMENT OF AN effective vaccine against the human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) is urgent and difficult. A successful vaccine must protect against cell-associated and cell-free virus at genital mucosal surfaces and in the bloodstream and must exert broad protection against the tremendous genetic variation exhibited by the virus. Because we do not understand the nature of protective immunity against HIV or have an animal model of HIV-1–induced disease, we must rely heavily on animal lentiviral infections to guide us toward a deeper understanding of the pathogenesis of the virus and the development of an effective AIDS vaccine.

The picture from the animal lentivirus models, however, is still unclear. Using recombinant HIV-1 envelope vaccines, a few chimpanzees have been protected against infection with a low dose of the homologous strain (IIIB) of HIV-1, apparently by the induction of a threshold level of neutralizing antibodies. Similar recombinant envelope vaccine approaches, however, have not been generally effective in protecting against challenge infection in the other animal lentivirus models. In these other animals, the best protection has been achieved with vaccines made of inactivated whole virus or attenuated live virus, but the mechanism of protection remains uncertain and such whole-virus approaches are not considered safe or practical for humans.

The shortfalls of these experimental vaccines are important: they require at least three injections over several months; the immunity is rather short-lived (less than a year); and the protection does not extend to intravenous challenge with higher doses of cell-free virus, to intravenous infection with cell-associated virus, or to infection across an intact genital mucosa. None of the experimental HIV-1 vaccines have yet been tested in chimpanzees against widely divergent HIV-1 strains such as occur in nature. In general, the immune protection elicited by the experimental vaccines in animals appears to convey a complete block to infection after challenge. This type of "sterilizing immunity" may be required of a vaccine to prevent later viral activation and disease, but it may also explain why the protection is so limited and why antiviral cytotoxic T-lymphocyte activity is not usually induced by these vaccines. The induction of strong $CD8^+$ cytotoxic T-lymphocyte activity is almost certainly a requirement of any truly efficacious HIV vaccine, and this may depend on a live vector or an attenuated live virus approach.

In the United States, seven different phase 1 and 2 trials, using candidate HIV-1 recombinant envelope vaccines and adjuvants, are under way in more than 500 volunteer uninfected people. Two trials use core peptides (p17 and p24), and one trial uses inactivated (gamma irradiation and β-propiolactone) envelope-deficient whole HIV-1. In general, these immunogens have proved safe and immunogenic, but they have induced mainly type-specific neutralizing antibody of short duration (less than 6 months) and low titer (less than that seen in natural infection) and no $CD8^+$ cytotoxic T-lymphocyte activity. Live vaccinia vaccine (HIV-recombinant envelope) priming followed a year later by boosting with an HIV-envelope subunit (expressed in baculovirus) has had some encouraging results, but the vaccinia vector would not be safe for large efficacy trials unless further attenuated. Also, live vaccinia vectors would not be effective in vaccinia-immune persons. None of these phase 1 or 2 HIV-1 vaccine candidates have elicited the strong, durable, broadly reactive humoral and cytotoxic T-lymphocyte immune responses needed to justify larger-scale efficacy trials.

On the optimistic side, several hundred HIV-seropositive but immunocompetent persons who have received the HIV gp160 vaccine after infection have generally responded favorably by generating antibodies and T cells that recognize new antigenic determinants in the envelope. Insufficient time has elapsed to determine whether this treatment will suppress viral replication and delay the onset of AIDS. Evaluating the safety and immunogenicity of various HIV-1 immunogens given to HIV-1–infected subjects will help determine the suitability of these materials for prophylactic vaccination.

The criteria for selecting vaccine candidates for efficacy trials are unsettled, and we must decide on the end points to be used: preventing infection or delaying or preventing disease. For the latter, we need to define surrogate markers to predict disease, such as quantitative virus load, that can be measured early after infection. It is hoped that further preclinical developments in the animal models using different viral immunogens, different adjuvants, different routes of antigen presentation (such as mucosal), novel live vectors